

CASE REPORT

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Diagnostic utility of metabolic exercise testing in a patient with cardiovascular disease

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Abstract

Disproportionate exercise limitation in patients with cardiovascular disease is a common problem faced by clinical cardiologists and other physicians. Symptoms may be attributed to psychological factors or hypothetical pathophysiological mechanisms that are difficult to confirm clinically. This case report describes how the use of metabolic exercise testing in a 28 year old woman with morphologically and haemodynamically mild hypertrophic cardiomyopathy and severe exercise limitation led to the diagnosis of an alternative cause for the patient's symptoms, namely a primary disturbance of the mitochondrial respiratory chain probably caused by a nuclear encoded gene defect.

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Keywords: metabolic exercise testing; mitochondrial disease; hypertrophic cardiomyopathy

A 28 year old married nurse presented with a history of progressive and refractory exertional dyspnoea, fatigue, and presyncope from the age of 13 years. There was no history of paroxysmal nocturnal dyspnoea, orthopnoea, or chest pain. At the age of 26 years, she had been treated for manic depression. Her identical twin had similar symptoms, her father had undergone aortic surgery, and her mother was asymptomatic. Clinical examination revealed sinus rhythm, blood pressure 110/60 mm Hg, a palpable atrial beat, a late systolic murmur at the left sternal edge, and a soft pansystolic murmur at the apex. ECG demonstrated normal sinus rhythm, left ventricular hypertrophy, ST segment depression, and T wave inversion in leads II, III, aVF, and V4-6 (fig 1). Forty eight hour ambulatory ECG monitoring demonstrated normal sinus rhythm with occasional ventricular ectopics (less than 30/hour, grade 2).

Two dimensional echocardiography demonstrated symmetric left ventricular hypertrophy (maximum 1.9 cm) with a left atrial diameter of 3 cm and left ventricular end diastolic and end systolic dimensions of 4.3 cm and 2.4 cm, respectively (fig 2). Peak left ventricular outflow velocity was 1.32 m/s. Treadmill exercise testing (Bruce protocol) to the limit of tolerance demonstrated an exercise time of 4.26 minutes, maximum heart rate 166 beats/min (86% predicted), and a peak oxygen uptake (VO_2) of 10.1 ml/min/kg (27% predicted¹). Respiratory gas analysis indicated the presence of an early onset metabolic acidemia. At peak exercise she complained of angina and severe dyspnoea.

Pulmonary function tests were normal and there was no radiographic evidence for interstitial lung disease (computed tomographic thorax scan) or pulmonary emboli (ventilation perfusion lung scan). Cardiac catheterisation demonstrated normal resting intracardiac pressures with no evidence for an intracardiac shunt. During upright cycle ergometry pulmonary capillary wedge pressure rose to 24 mm Hg and cardiac index to 6.62 l/m² with no evidence of arterial desaturation. Rapid incremental upright cycle ergometer testing to the limit of tolerance with sampling of arterialised venous blood from the dorsum of a heated hand confirmed the low peak VO_2 , low maximum heart rate, and a premature onset of

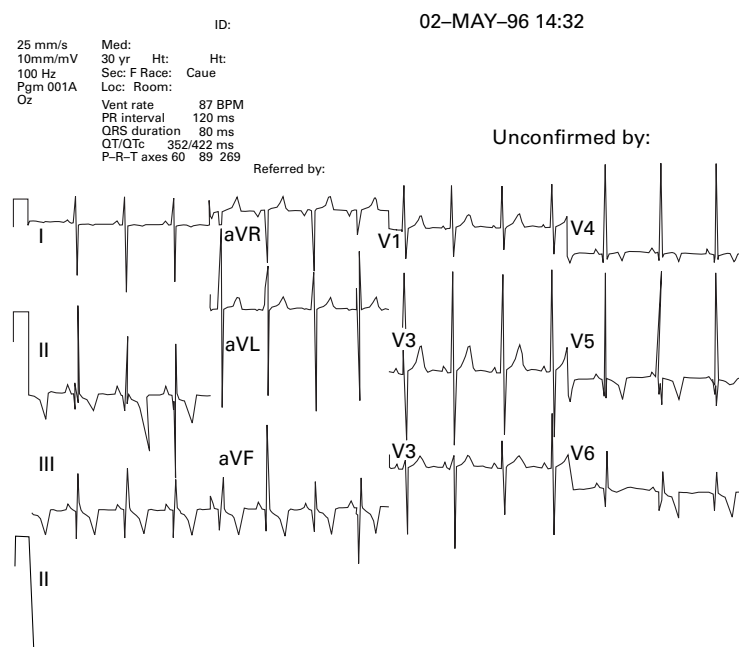


Figure 1 Twelve lead ECG (25 mm/s) in patient demonstrating left ventricular hypertrophy.

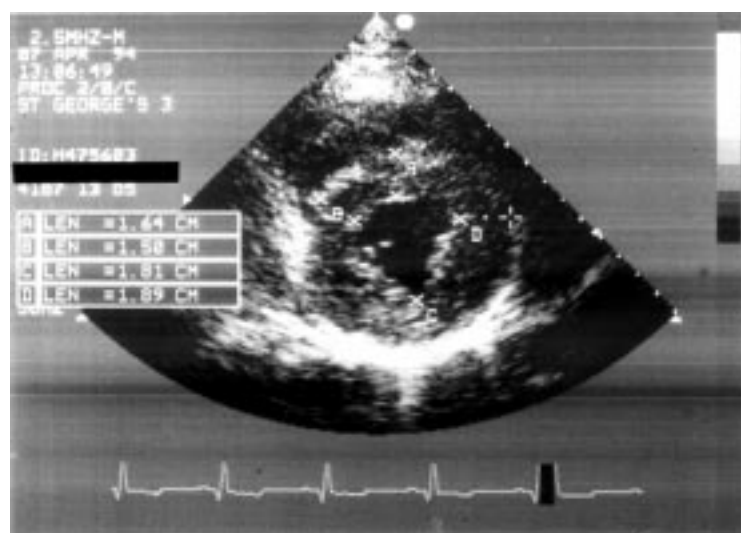


Figure 2 Two dimensional echocardiogram showing parasternal short axis view of the left ventricle and concentric left ventricular hypertrophy.

metabolic (lactic) acidaemia—that is, low lactate threshold (fig 3). The oxygen pulse ($\text{VO}_2/\text{heart rate (HR)}$)² was severely compro-

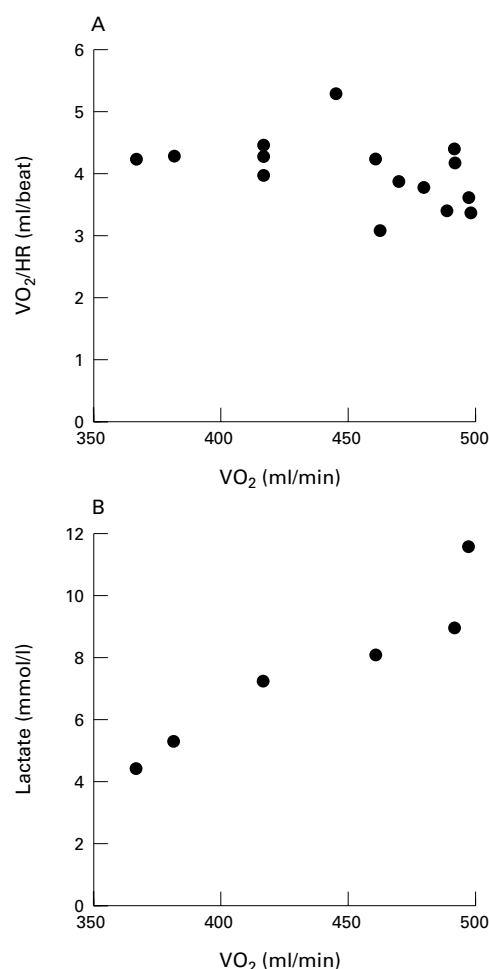


Figure 3 Results of upright bicycle ergometry. (A) Change in oxygen pulse (VO_2/HR) as a function of oxygen uptake (VO_2). (B) Responses in arterialised venous lactate (from dorsum of heated hand) with increasing workload. The initial three samples were taken at zero load at 20, 40, and 60 revolutions/min.

Table 1 Respiratory chain enzyme analysis in patient compared to 10 age matched controls for each complex. Values are expressed as a ratio to citrate synthase (nmol/min/unit citrate synthase)

	Patient	Control (mean (SD))
Complex I	0.01	0.25 (0.06)
Complex II	0.29	0.37 (0.09)
Complex III	0.74	1.43 (0.28)
Complex IV	0.16	1.31 (0.40)

mised at rest (4 ml O_2/beat), and did not rise with increasing workrate (fig 3).

Neurological examination was normal with no evidence of fundal abnormalities, or ocular or skeletal myopathy. Nerve conduction studies were normal, but widespread muscle sampling at electromyography demonstrated small polyphasic motor units with early recruitment consistent with a chronic myopathy.

An open muscle biopsy from the vastus lateralis was performed. Light microscopy demonstrated a homogeneous reduction in cytochrome c oxidase (COX) activity (complex IV of the respiratory chain). Staining with succinate dehydrogenase and Gomori trichrome stains showed mitochondrial proliferation ("ragged red fibres") in 2% of fibres. Electron microscopy confirmed mitochondrial proliferation and demonstrated paracrystalline inclusions.

Mitochondria were isolated from the skeletal muscle biopsy and the respiratory chain enzymes were assayed and compared to 10 age matched controls (table 1). Deficiencies in complex I, III, and IV activity were present.

Total DNA was extracted from muscle using standard methods.³ Southern blotting excluded a large scale rearrangement of mitochondrial DNA (mtDNA).⁴ All mitochondrial transfer RNA (tRNA) and mitochondrial COX genes were sequenced using an automated DNA sequencer. No changes from the published sequence were identified.⁵

Discussion

Clinically, the most important abnormality detected in this case was a disproportionately poor exercise tolerance. The low peak VO_2 and the early onset of metabolic acidaemia observed during symptom limited incremental exercise testing argued strongly for compromised peripheral oxygen delivery. The lack of an appreciable increase in the O_2 pulse (which by Fick's law represents the product of stroke volume and the arterio-mixed venous O_2 content difference) with increasing work rate was suggestive of impaired cardiac function and/or reduced peripheral oxygen extraction.² In view of the normal cardiac index during exercise, the latter was most likely. While studies have shown that the majority of patients with hypertrophic cardiomyopathy have mutations in one of several genes encoding cardiac sarcomeric proteins,⁶ a number of other rare genetically determined disorders can produce a cardiac phenotype identical to that seen in hypertrophic cardiomyopathy. Primary dysfunction of the mitochondrial enzyme systems responsible for oxidative phosphorylation causes a range of multisystem diseases,

affecting particularly skeletal muscle and the central nervous system.⁷ Cardiac involvement is usually associated with more extreme clinical phenotypes such as Kearns-Sayre syndrome (ophthalmoplegia, atypical retinitis pigmentosa, mitochondrial myopathy, cardiac conduction disease), myoclonic epilepsy with ragged red fibres (MERRF), and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS).

This case is unusual in that the cardiomyopathy occurred in the absence of clinically evident (although histologically proven) neuromuscular involvement. Genetically determined oxidative phosphorylation disease can be classified into four groups: presumed nuclear mutations; mtDNA point mutations; mtDNA deletions and duplications; and undefined disorders.⁷ Many oxidative phosphorylation disorders result from point mutations in mtDNA (often showing "maternal" inheritance) or mtDNA deletions. While biochemical analysis confirmed a respiratory chain defect in complexes I, II, and IV, the striking abnormality in the present case was that all muscle fibres demonstrated a reduction in COX staining as well as showing some ragged red fibres. This is an unusual finding in an adult patient, and the pattern of COX staining is entirely different from the mosaic distribution of COX activity typically seen in patients with primary mtDNA defects. Since extensive mitochondrial DNA analysis excluded all described mtDNA mutations and ruled out point mutations in all tRNA and mitochondrial COX genes, it is likely that the COX deficiency was caused by an as yet unidentified nuclear gene defect.

Left ventricular hypertrophy occurs in a number of disorders with distinct pathophysiology and implications for patient manage-

ment. Differentiation of these diseases is facilitated by an integrated clinical assessment that includes pedigree analysis, physical examination, and objective measures of cardiopulmonary function. The presence of severe lactic acidosis in conjunction with abnormal skeletal muscle histology and biochemistry in this case are definitive evidence for a "mitochondrial myopathy". The fact that the patient also had concentric hypertrophy makes it almost certain that she also had a mitochondrial "cardiopathy". Mitochondrial disease affecting heart and skeletal muscle should be considered as a differential diagnosis in all patients with morphologically and haemodynamically mild left ventricular hypertrophy that present with severe exercise limitation and a low anaerobic threshold, even if clinical neuromuscular signs are absent.

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